REMARKS

A. Status of the Claims

Claims 1-3 were originally filed with the case on December 5, 2003. Claims 1-3 were rejected in an Official Action mailed on November 17, 2004. Claims 1 and 3 were amended and claims 4-7 were added in a Response to Office Action filed on May 17, 2005. All claims were rejected in an Official Action mailed on July 29, 2005. No claims were amended, added, or canceled in the Response to Office Action filed on November 29, 2005. All claims were rejected in an Official Action mailed on March 9, 2006. No claims were amended, added, or canceled in the Response to Office Action filed on September 8, 2006. Claims 1-7 are rejected in the present Office Action. No claims are amended, added, or canceled herein. Applicants thank the Examiner for the previous consideration of our submissions.

B. The Claims are not Obvious under 35 U.S.C. § 103(a).

The Action rejects all claims under 35 U.S.C. 103(a) as being obvious over Malfroy-Camine et al. (6,064,188) in view of LaHaye et al. (5,075,116), Crapo et al. (5,994,339), Campbell and Winkler et al. (Molecular Vision 1999). Malfroy-Camine is said to teach the antioxidant and superoxide dismutase activity of the claimed compounds. The first Action acknowledges that Malfroy-Camine lacks a teaching the treatment of macular degeneration, diabetic retinopathy or retinal edema. LaHaye is said to teach the use of free radical scavengers and antioxidants for treating diseases such as macular degeneration. Campbell is said to teach that injection is a routine route of ophthalmic administration. The second Action acknowledges that Campbell lacks a teaching of the use of the compounds described to treat ocular disorders such as macular degeneration. Crapo is said to teach that compounds having superoxide dismutase activity have previously been used for the treatment of AMD. Winkler is said to teach that there is a correlation between oxidation and macular

degeneration and the effect of superoxide dismutase in preventing oxidative damage. The Action suggests that the combination of these references would have made obvious to one skilled in the art the use of the claimed compounds having superoxide dismutase activity for the treatment of conditions associated with oxidative damage such as AMD. Applicants respectfully traverse.

Determining obviousness requires an analysis of the invention *as a whole*. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990). It is well settled patent law that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *See In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); MPEP § 2143.01. In addition, the Federal Circuit held in *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Mills*, 16 U.S.P.Q.2d at 1432; *see also* MPEP § 2143.01, page 2100-91

The combination of the cited references does not teach or suggest the claimed invention, nor is there any teaching, suggestion, or motivation in these references that would produce the claimed invention. The present invention is directed to the use of mimics of the enzyme superoxide dismutase to treat persons suffering from the exudative and non-exudative forms of AMD, diabetic retinopathy, which includes proliferative diabetic retinopathy, and retinal edema. The compounds claimed for use in the present invention are superoxide dismutase mimetics, which are administered topically, by ocular injection, or

parenterally, to the eye of the patient suffering from such disorders. While Malfroy-Camine does recognize that certain salen-metal compounds exhibit antioxidant and superoxide dismutase activity, it does not teach or suggest the treatment of macular degeneration, diabetic retinopathy or retinal edema. The combination of the other cited references does not cure this deficiency in Malfroy-Camine.

The Action asserts that Campbell teaches injection is a routine route for ophthalmic administration. However, the structure of the compounds taught in Campbell is so different compared to the compounds of the instant claims that one of skill in the art would not have been motivated to look to Campbell for an administration route. Thus, Campbell does not give an adequate motivation to combine with any of the other references cited in the Action.

The Action cites LaHaye and Crapo as supposedly teaching that small or large compounds having superoxide dismutase activity have been previously used for the treatment of AMD. However, these references do not cure the deficiencies of Malfroy-Camine, because the compounds to which they refer are so dissimilar to the claimed compounds.

The Action cites Crapo as supposedly teaching that structurally similar compounds having superoxide dismutase activity have been previously used for the treatment of macular degeneration. However, Crapo teaches that two qualities of the compounds therein are important for therapeutic activity, which the compounds of the present invention lack. The first is that the Crapo compounds are designed as extracellular-targeted oxidants to mimic the function of extracellulary-expressed SOD isoform EC-SOD, as evidenced by the following text from the Crapo specification (all italics are added):

> The invention thus relates to methods of manipulating nitric oxide function that involve the use of *extracellular antioxidants* (column 2, lines 35-38);
>
> In one embodiment, the present invention relates to an oxidant scavenger, for example, a mimetic of superoxide dismutase, catalase or peroxidase, comprising a nitrogen-containing macrocyclic moiety *and a cell surface or extracellular matrix*

> *targeting moiety*, or a pharmaceutically acceptable salt thereof. (column 2, lines 59-65);
>
> Targeted forms of the mimetics can be produced by coupling the porphine directly or via a linker to a cell surface or extracellular matrix targeting moiety, for example, as indicated above in the definition of R4. The targeted mimetics can be used, for example, to mimic EC-SOD.
>
> In another embodiment, the present invention relates to a method of treating a pathological condition of a patient (eg, of the lungs of a patient) resulting from superoxide radical-induced degradation of nitric oxide. *The method comprises administering to the patient (eg, to the airways of the patient) an effective amount of a compound having the activity and tissue specificity of SOD (eg EC-SOD)* under conditions such that the treatment is effected. (column 6, lines 14-21)

The compounds of the present invention are not designed as extracellularly-accumulating SOD mimics. In fact, they are cell membrane-permeable, and are designed as analogs of the mitochondrially-expressed SOD-2 enzyme [see for example Salvemini *et al.*, *Nature Reviews Drug Discovery* **2002**, *1*(5), 367-374]. Thus, if the alleged utility of the extracellularly-targeted Crapo compounds in treating AMD were due to detoxification of extracellularly-accumulating superoxide, one skilled in the art would not reasonably extrapolate a similar action for the cell-permeable, non-targeted compounds of the instant invention.

The second Crapo teaching that diverges from the compounds of the present invention is that the Crapo compounds' mechanism of action is due, not only to superoxide dismutase activity, but also to their ability to detoxify other reactive oxygen species, such as hydrogen peroxide, as evidenced by the following text from the Crapo specification (italics added):

> One embodiment of the present invention relates to a method of regulating extracellular nitric oxide levels using polypeptides having EC-SOD activity. As indicated above, the invention also relates to mimetics of EC-SOD that can be targeted to strategic locations and to the use of such mimetics in manipulating extracellular levels of nitric oxide. The invention, however, is not limited to nitric oxide manipulation as the sole mechanism of action of the compounds, mimetics,

etc, of the invention. *Rather, the invention relates to oxygen radical, hydrogen peroxide and peroxynitrite scavenging generally*. (column 26, lines 12-22);

The present invention relates to a method of modulating intra- or extracellular levels of oxidants such as superoxide radicals, *hydrogen peroxide* and peroxynitrite. More particularly, the invention relates to a method of modulating normal or pathological processes involving superoxide radicals, *hydrogen peroxide*, nitric oxide or peroxynitrite using low molecular weight antioxidants, for example, mimetics of SOD, *catalase* or peroxidase. (column 2, lines 51-58);

In one embodiment, the present invention relates to an oxidant scavenger, for example, a mimetic of superoxide dismutase, *catalase or peroxidase*, comprising a nitrogen-containing macrocyclic moiety and a cell surface or extracellular matrix targeting moiety, or a pharmaceutically acceptable salt thereof. (column 2, lines 59-65);

FIG. 31 shows a second order rate constant plot for *catalase mimetics*. (column 10, lines 62-63);

FIG. 32 shows the effect of *MnTBAP on H_2O_2 -induced endothelial injury*. (column 10, lines 64-65);

FIGS. 33A and 33B show *the reduction by MnTBAP and MnTmPyP of endothelial cell injuries caused by exposure to glucose oxidase-produced hydrogen peroxide*. FIG. 33C shows that *ZnTBAP does not reduce hydrogen peroxide-induced endothelial cell injury*. FIG. 33D shows that *endothelial cells are not protected from hydrogen peroxide-induced injury by CuZnSOD*. (column 10, lines 66-67 through column 11, lines 1-5);

In contrast, the SOD mimics of the present invention, derived from Riley *et al.* US Patent 6,214,817, do not react at an appreciable rate with other reactive oxygen species, such as hydrogen peroxide, peroxynitrite, oxygen, or hypochlorite (Salvemini *et al.*, *Nature Reviews Drug Discovery* **2002**, *1*(5), 367-374). This is important because hydrogen peroxide is itself generated by the detoxification of superoxide by an SOD mimic, peroxides are toxic to retinal epithelial cells (see for example figure 13 on p. 40 of Winkler *et al.*), and catalase activity (important for detoxifying hydrogen peroxide) has been shown to decrease with age and AMD status (Liles *et al.*, *Archives of Ophthalmology* **1991**, *109*(9), 1285-1288; Yildirim *et al.*, *Opthalmologica* **2004**, *218*(3), 202-206). Thus, if the anti-AMD therapeutic effect alleged for the Crapo compounds is due partly to their admitted ability to detoxify other

reactive oxygen species such as hydrogen peroxide, one skilled in the art would not reasonably extrapolate the SOD mimics of the instant invention to have a similar effect, for they are unable to detoxify co-generated hydrogen peroxide, as well as any other pathological reactive oxygen species.

Furthermore, Applicants respectfully submit that from a chemical structure basis Crapo is irrelevant in view of the instant claims, because the compounds taught in Crapo are dissimilar to the claimed compounds. Crapo relates to a very particular class of SOD mimetics, and teaches that the mimetics could be used for the treatment of macular degeneration. The Action asserts that the compounds in Crapo are similar to the claimed compounds, which is not the case. The claimed compounds are salen-metal complexes, while the compounds in Crapo are porphyrin-containing compounds. The primary structural similarity of the claimed compounds with the compounds in Crapo arises from the manganese ion common to each group of structures. As an infinite number of compounds could use manganese ions as their functional site, this basic similarity is not sufficient to support an inference of motivation. One of skill in the art would not have been motivated to use the lower molecular weight salen-metal complexes for any purpose based on the disclosure and discussion of porphyrin-containing compounds in Crapo.

In addition, the claimed compounds satisfy one of the objects of the present invention, which is to provide lower molecular weight compounds that catalyze superoxide disproportionation with efficiency comparable to endogenous Mn SOD, while avoiding the bioavailability and immunogenic issues thought to be due to the higher molecular weight species (Spec. page 6, lines 18-25). The lower molecular weight of the claimed compounds has a direct effect on the potential bioavailability improvements, and is an essential component of the uniqueness of the present invention. Thus, the claimed compounds are further distinguished from the compounds of Crapo.

LaHaye discusses the use of a composition of small antioxidant vitamins to treat macular degeneration. Antioxidant vitamins belong to the chain-breaking category of antioxidants. Chain-breaking antioxidants neutralize free radicals by donating one of their own electrons, thereby ending the electron "stealing" reaction in which free radicals steal electrons from other molecules and create more unstable free radicals down the chain. The present invention is directed to the use of superoxide dismutase mimics, which are complexed with manganese. Superoxide dismutase belongs to the enzyme category of antioxidants. Enzyme antioxidants prevent oxidation by reducing the rate of chain initiation. By scavenging initiating radicals, such antioxidant enzymes can thwart an oxidation chain from ever setting in motion. LaHaye discusses only the effect of antioxidant vitamins for the treatment of macular degeneration and makes no suggestion that antioxidant compounds complexed with transition metals could be used to treat ocular diseases. One of skill in the art would not have been motivated to use the antioxidant enzyme mimics of the present invention for any purpose based on the discussion of chain-breaking antioxidant vitamins in LaHaye.

Because the compounds in LaHaye and Crapo are so dissimilar to the claimed compounds, these references cannot be used to provide a link between the teachings of Malfroy-Camine to the present invention.

Nonetheless, the Action asserts that the present claims are obvious because Winkler supposedly teaches the role of oxidation in relation to macular degeneration and the effect of superoxide dismutase in preventing oxidative damage caused by macular degeneration. Applicants respectfully submit that, based on the entirety of the prior art available at the time the invention was made, there was no reasonable expectation of success for using superoxide dismustase for treating macular degeneration based on Winkler, and the invention is therefore not obvious.

An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *KSR Intn'l Co. v. Teleflex Inc.*, No. 04-1350, 550 U.S. ___ (2007); *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). The Action states that obviousness does not require absolute predictability. However, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986).

At the time the present invention was made, Winkler was one of several references that discussed the potential role of superoxide dismutase in preventing oxidative damage and the correlation between oxidative damage and AMD. Winkler discusses superoxide dismutase only as one of a number of oxidants that may play a role in AMD progression. Superoxide dismutase is identified in Winkler as a potential protectant of molecules damaged by oxidation, along with sunglasses and the series of non-enzyme antioxidants. Winkler focuses the majority of its discussion on studies involving these non-enzyme antioxidants including glutathione (GSH), vitamin C, vitamin E, and carotenoids. While the paper does suggest that superoxide dismutase may be involved in preventing oxidative damage, it provides no methodology for how superoxide dismutase could be used to treat macular degeneration nor does it provide any research to support its assertion that the enzyme may play a role in AMD progression.

Though Winkler did not provide research data to support its assertion, there were other references available at the time the invention was made that provided empirical evidence that there was no association between superoxide dismutase activity and AMD. Based on the lack of support provided by Winkler and the abundance of evidence given in the other controverting references, it should be clear that Winkler provided no reasonable expectation of success for using superoxide dismutase to treat macular degeneration.

Both De La Paz (British Journal of Ophthalmology 1996) and Delcourt (Ophthalmology 1999) involve research studies in which blood samples were taken from a group of participants in order to statistically analyze the levels of superoxide dismutase activity in comparison to the severity of AMD. The De La Paz study included 66 participants, 54 of whom showed varying levels of severity of aging maculopathy. The paper concluded based on multiple regression analysis and ordinal logistic regression analysis that there is no significant association between disease severity of AMD and superoxide dismutase activity. The Delcourt study included 2,156 participants for its analysis of AMD and antioxidant enzymes, 38 of whom had late AMD. The paper concluded, based on similar statistical analyses, that high levels of erythrocyte superoxide dismutase activity were not associated with late AMD and early signs of AMD.

While both De La Paz and Delcourt acknowledged that oxidative mechanisms may play a role in the development of AMD and that superoxide dismutase is involved in protecting against such oxidative damage, each provided statistical data that higher levels of the enzyme do not affect the severity of AMD. Like Winkler, neither of these references showed that superoxide dismutase could be used to treat macular degeneration. Although the references recognize that superoxide dismutase is involved in protecting against oxidative damage such as that which potentially leads to AMD, there is no indication that higher levels of the enzyme could be used to treat the disease. In fact, these papers seemed to suggest that

an increase in the amount of the enzyme would have no effect because there is no association between the severity of AMD and the amount of superoxide dismutase activity. Thus, these papers appear to teach away from the use of superoxide dismutase for treating macular degeneration. Winkler does not provide or discuss any data that refute the data or conclusions in De La Paz or Delcourt. Consequently, one of skill in the art would not have been motivated to use compounds with superoxide dismutase activity for treating macular degeneration, since there would have been no reasonable expectation that the use of such compounds for that purpose would be successful.

In order to support a 103 rejection of the instant claims, the cited references must teach or suggest a method for treating AMD, DR, and/or retinal edema via administration of the described compounds. The Action does not provide an adequate or sufficiently explicit explanation of why one skilled in the art in view of Malfroy-Camine, Campbell, LaHaye, Crapo, and Winkler would expect that the salen-metal complexes described in the present invention would effectively treat these ocular disorders.

In light of the foregoing arguments, Applicants respectfully request that the obviousness rejection be withdrawn.

C. Conclusion

This is submitted to be a complete response to the outstanding Action. The Examiner is invited to contact the undersigned attorney at (817) 615-5330 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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